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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/360,934 | 07/26/1999 | ANTONELLO COVACCI | CHIR-0158 | 4878 |

27476 7590 06/20/2005

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| EXAMINER | |
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| DEVI, SARVAMANGALA J N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/360,934 | COVACCI ET AL. | |
| | Examiner | Art Unit | |
| | S. Devi, Ph.D. | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *40,54,61-65,72-75,82-86,93 and 94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,54,61-65,72-75,82-86,93 and 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## Response to Applicants' Amendment

## Applicants' Amendment

**1)** Acknowledgment is made of Applicants' amendment filed 04/04/05 in response to the non-final Office Action mailed 11/03/04.

## Status of Claims

**2)** Claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 have been amended via the amendment filed 04/04/05.

Claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 are pending and are under examination.

## Prior Citation of Title 35 Sections

**3)** The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

## Prior Citation of References

**4)** The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

## Rejection(s) Withdrawn

**5)** The rejection of claims 40, 63 and those dependent therefrom made in paragraph 14 of the Office Action mailed 11/03/04 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn. A modified rejection to cover the claims, as amended, is set forth below.

**6)** The rejection of claims 61, 62, 72, 73, 82, 83, 93 and 94, and those dependent therefrom made in paragraph 15 of the Office Action mailed 11/03/04 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendments to the claims. A modified rejection to cover the claims, as amended, is set forth below.

**7)** The rejection of claims 40 and 63 made in paragraph 16(a) of the Office Action mailed 11/03/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claims.

**8)** The rejection of claims 54, 61, 62, 64, 65, 72, 73, 82, 83, 85, 86, 93 and 94 made in paragraph 16(b) of the Office Action mailed 11/03/04 under 35 U.S.C. § 112, second paragraph, as

being indefinite, is withdrawn in light of Applicants' amendments to the base claim.

**9)** The rejection of claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 made in paragraph 18 of the Office Action mailed 11/03/04 under 35 U.S.C. § 102(e)(2) as being anticipated by Cover *et al.* (US 6,054,132, filed 02/26/1992 - already of record) (Cover *et al.*, '132) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A Laboratory Manual.* Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988), is withdrawn in light of the new ground of rejection made below.

**10)** The rejection of claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 made in paragraph 19 of the Office Action mailed 11/03/04 under 35 U.S.C. § 102(b) as being anticipated by Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992 – already of record) (Cover *et al.*, 1992) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A Laboratory Manual.* Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988), is withdrawn in light of the new ground of rejection made below.

**11)** The rejection of claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 made in paragraph 20 of the Office Action mailed 11/03/04 under 35 U.S.C. § 102(b) as being anticipated by Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992 – already of record) (Cover *et al.*, 1992) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A Laboratory Manual.* Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988), is withdrawn in light of the new ground of rejection made below.

## Rejection(s) Maintained

**12)** The provisional rejection of claims 40, 54, 63-65, 74, 75, 84 and 85 made in paragraph 10 of the Office Action mailed 06/09/03 and maintained in paragraph 22 of the Office Action mailed 02/25/04, paragraph 11 of the Office Action mailed 11/03/04 and paragraph 11 of the Office Action mailed 11/03/04 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38, 44, 45 and 46 of the co-pending application SN 09/921,157, is still maintained for reasons set forth therein. Applicants have assured the Office that they would submit a terminal disclaimer over SN 09/921,157 upon the receipt of an indication of allowability.

**13)** The rejection of claims 74, 75 and 84-86 made in paragraph 14 of the Office Action mailed 11/03/04 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is maintained for reasons set forth therein and herebelow.

Applicants contend that the specification at page 5, lines 31-39, teaches that the term cytotoxin or toxin is a general term referring to the protein of *Helicobacter pylori*. Applicants state

that this passage clearly teaches that the precursor protein (which has the amino acid sequence of SEQ ID NO: 3) is a protein of 140 kDa and that the proteolytic fragment has cytotoxic activity (by clear implication and generally accepted terminology in the art, the precursor does not have such activity). Applicants submit that lines 1-11 on page 6 describe the processed fragment being recovered from supernates and having cytotoxic activity. Applicants claim that they are the ones who for the first time discovered that the cytotoxin is actually a processed portion of a much larger precursor protein. Applicant conclude that one of skill in the art would understand that the precursor protein (having the amino acid sequence of SEQ ID NO: 3) would not be cytotoxic until processed, and thus the polypeptide of SEQ ID NO: 3 would not have cytotoxic activity. Applicants further cite the post-filing references of Vinion-Dubiel *et al.* (1999); McClain *et al.*, 2003; Reyrat *et al.*, 1999; and Genisset *et al.* and state that these references prove that the cytotoxin of *H. pylori* may be altered genetically to produce a cytotoxin that has substantially reduced or no cytotoxicity. Applicants state that this was first taught in the Applicants' specification and has now been borne out by these investigators' work. Applicants assert that the specification teaches that a polypeptide that is 'derived from' a particular nucleic acid sequence is one that has an amino acid sequence encoded by the nucleic acid, is a portion of the encoded sequence, or is immunologically identifiable with a polypeptide encoded in the sequence. Applicants state that those of skill in the art would clearly understand that these are not mutually exclusive, despite the Office's overemphasis of the word 'or'. Applicants further state that one of skill in the art would appreciate that not all fragments of the encoded sequence would necessarily be immunologically identifiable with the encoded sequence. Applicants opine that the conjunction 'and' would be inappropriate to express the idea that Applicants convey in the specification. Applicants state that this 'is merely an attribute of the encoded polypeptides and certain polypeptide fragments would be immunologically identifiable with the encoded sequence'. Applicants contend that all the immunologically identifiable fragments would be at least 3-5, 8-10, or 11-15 amino acids in length and pose the question: 'How could it be otherwise'? Applicants state that it is puzzling that the Office is not persuaded that the original claim 8 supports the subject matter that the polypeptides have the two functional aspects of being immunologically identifiable with antibodies that react specifically with the full-length protein (SEQ ID NO: 3) and which have no or reduced cytotoxicity. Applicants contend that the original claim 8 adds the limitation that the polypeptides have no or reduced cytotoxicity, or substantially

reduced cytotoxicity, and therefore the claims, as originally filed, clearly contemplated the precursor and fragments of the polypeptide having no or reduced cytotoxicity. Applicants state that the portions of the amino acid sequence were also said to include those that were immunologically identifiable with the encoded protein.

Applicants' arguments have been carefully considered, but are non-persuasive. The descriptive support for the claim limitations has to come from Applicants' specification, as originally filed, and not from the post-filing references of Vinion-Dubiel *et al.* (1999); McClain *et al.*, 2003; Reyrat *et al.*, 1999; and Genisset *et al.* Contrary to Applicants' assertion, the specification at page 5, lines 31-39, does not teach that the term cytotoxin or toxin is a 'general term' referring to the protein of *Helicobacter pylori.* This part of the specification does not associate a precursor cytotoxin having the amino acid sequence from Figure 2 (i.e., SEQ ID NO: 3) to 'reduced cytotoxic activity' or 'no cytotoxic activity'. Contrary to Applicants' assertion, lines 1-11 on page 6 do not describe any fragment 'being recovered from supernates and having cytotoxic activity'. Contrary to Applicants' contention, lines 1-11 on page 6 of the specification describe a 87 kDa polypeptide 'previously described' by Cover *et al., J. Biol. Chem.* 267: 10570-75, 1992. Furthermore, Applicants' express argument that the precursor protein having the amino acid sequence of SEQ ID NO: 3 would not be cytotoxic until processed and thus the polypeptide of SEQ ID NO: 3 would not have cytotoxic activity, provides the *prima facie* evidence for lack of support for a polypeptide of SEQ ID NO: 3 or a fragment thereof that is immunologically identifiable as recited *and* that exhibits 'reduced cytotoxic activity compared with *Helicobacter pylori* cytotoxin purified from cell cultures'. How can a polypeptide of SEQ ID NO: 3 which is asserted to have no cytotoxic activity exhibit 'reduced cytotoxic activity compared with *Helicobacter pylori* cytotoxin purified from cell cultures'?

The specification at lines 21-30 of page 14 describes a polypeptide which consists of at least 3-5 amino acids, and more preferably at least 8-10 amino acids, and even more preferably at least 11-15 amino acids, **or** a polypeptide which is immunologically identifiable with a 'polypeptide encoded in the sequence'. The limitation 'and' appearing between parts (i) and (ii) of the instant claims requires that the claimed polypeptide or fragment thereof have the function recited in part (i) **and** the function recited in part (ii) of the claim. The recitation 'or' in the specification is given its normal meaning. Applicants appear to insist that the Office should interpret the limitation 'or' as

being equivalent to the term 'and'. However, doing so would be improper under the procedure permitted within MPEP.

The original claim 8, and claims 3, 2 and 1 from which it depends, are reproduced below [underlining in original]:

> 8. The recombinant protein according to claim 2 or 3 wherein the recombinant protein exhibits substantially no toxicity, or substantially reduced toxicity.
> 3. The recombinant protein according to claim 2 wherein the cytotoxin, precursor, derivative or fragment thereof has the amino acid sequence of Figure 2, or a portion thereof.
> 2. The recombinant protein according to claim 1 wherein the protein is a Helicobacter pylori cytotoxin or a precursor, derivative or fragment thereof.
> 1. A recombinant Helicobacter pylori protein, or a derivative or fragment thereof.

Thus, the recombinant *Helicobacter pylori* cytotoxin protein or a precursor, derivative or fragment thereof having 'the amino acid sequence of Figure 2', or a portion thereof claimed in these original claims, particularly claim 8, is not associated with immunological identifiability by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3. These original claims, including claim 8, are not drawn to a recombinant cytotoxin having a molecular weight range of 'at least 87 kDa to about 140 kDa' wherein the recombinant cytotoxin polypeptide comprises amino acid substitutions to form an altered polypeptide which exhibits no cytotoxic activity or reduced cytotoxic activity compared with *Helicobacter pylori* cytotoxin purified from cell cultures. The product claimed in these original claims is not associated with the two functions that are recited in the instant claims. These original claims and the description at lines 20-23 on page 8 of the specification do not include the limitation, 'amino acid substitutions', currently added to claims 61, 62, 72, 73, 82, 83, 93 and 94, let alone associate the claimed polypeptide with no cytotoxicity or reduced cytotoxicity and immunological identifiability by antibodies reactive specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3. Furthermore, Figure 2 recited in claim 3 depicts one single amino acid sequence that is 1296 amino acid residues-long. This single polypeptide sequence from Figure 2 can either be the amino acid sequence of the precursor cytotoxin or the cytotoxin itself. The single polypeptide of SEQ ID NO: 3 from Figure 2 cannot represent both a cytotoxic cytotoxin and a non-cytotoxic or less cytotoxic precursor cytotoxin. The description of the drawings at lines 28 and 29 of page 4 of the specification describes that Figure 2 represents SEQ ID NO: 3, 'the amino acid sequence for the cytotoxin (CT) protein'. One of skill in the art would understand the described 'cytotoxin (CT) protein' to be cytotoxic. The Figure 2 description does not identify SEQ ID NO: 3 to be the cytotoxin precursor.

However, on page 7 of their amendment filed 04/04/05, Applicants assert that the amino acid sequence of SEQ ID NO: 3 represents the 140 kDa full length precursor cytotoxin, which requires proteolytic processing to generate the cytotoxic protein. The single amino acid sequence from Figure 2 does not represent a polypeptide having the recited range of molecular weight and further having any generic or specific 'amino acid substitutions' and concurrently having the function of immunological identifiability by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3. For the reasons delineated above, the rejection set forth below is proper.

**14)** The rejection of claims 74 and 84 made in paragraph 16(a) of the Office Action mailed 11/03/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and herebelow.

Applicants contend that they have amended independent claims 74 and 84 to include the feature that the polypeptides have reduced cytotoxicity with respect to *Helicobacter pylori* cytotoxin purified from cell cultures. However, no such feature or limitation has been added to claims 74 and 84.

**15)** The rejection of claims 75, 82, 83, 85, 86, 93 and 94 made in paragraph 16 and 16(b) of the Office Action mailed 11/03/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and above in paragraph 14.

## Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

**16)** Claims 40, 63 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 40, as amended, includes the new limitations: 'purified' recombinant polypeptide comprising at least ten contiguous amino acids from the amino acid sequence of SEQ ID NO: 3, which polypeptide is immunologically identifiable by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3 and exhibits no cytotoxic activity or reduced cytotoxic activity 'compared with *Helicobacter pylori* cytotoxin purified from cell cultures'. Claim 63, as amended, includes the new limitations: 'purified' recombinant polypeptide

expressed from at least fifteen contiguous nucleotides of nucleotide sequence of SEQ ID NO: 2, which polypeptide is immunologically identifiable by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3 and exhibits no cytotoxic activity or reduced cytotoxic activity 'compared with a native *Helicobacter pylori* cytotoxin'. Applicants do not point to a specific portion of the specification for descriptive support for the limitations: 'compared with *Helicobacter pylori* cytotoxin purified from cell cultures' and 'compared with a native *Helicobacter pylori* cytotoxin'. Applicants' express argument on page 7 of their amendment/response filed 04/04/05 that 'the polypeptide having the amino acid sequence of SEQ ID NO: 3 ***is not itself cytotoxic***' [Emphasis in original] provides the *prima facie* evidence that a purified full length polypeptide of SEQ ID NO: 3, or a polypeptide comprising an at least five, ten or fifteen amino acids from SEQ ID NO: 3 which is immunologically identifiable as recited and exhibiting 'reduced cytotoxicity compared with *Helicobacter pylori* cytotoxin purified from cell cultures' or 'compared with a native *Helicobacter pylori* cytotoxin', is not supported in the instant specification. A review of the specification indicates that the new limitations added at the end of the claims are not supported. Therefore, the limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or point to specific pages and line numbers in the specification, as originally filed, where support for such recitations can be found.

**17)** Claims 61, 62, 72 and 73 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 61, 62, 72 and 73 include the new limitations: 'purified' recombinant polypeptide of claim ..... having a molecular weight of at least 87 kDa or at least 100 kDa 'to about 140 kDa wherein said polypeptide comprises amino acid substitutions to form an altered polypeptide wherein said altered polypeptide exhibits no cytotoxic activity or reduced cytotoxic activity compared with

*Helicobacter pylori* cytotoxin purified from cell cultures'. Accordingly, the claims are now drawn to a purified recombinant polypeptide comprising at least ten or fifteen contiguous amino acids from the amino acid sequence of SEQ ID NO: 3, which polypeptide is *required* to have a molecular weight falling within the range of at least 87 kDa or at least 100 kDa to about 140 kDa, and amino acid substitutions (i.e., any number of substitutions) to form an altered polypeptide which is *required* to exhibit immunological identifiability by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3 and exhibit no cytotoxic activity or reduced cytotoxic activity compared with *Helicobacter pylori* cytotoxin purified from cell cultures. Applicants point to lines 19-29 of page 16 of the specification as providing descriptive support for the term 'purified'. However, Applicants do not point to a specific portion of the specification for descriptive support for the limitation: 'compared with *Helicobacter pylori* cytotoxin purified from cell cultures'.

Applicants point to lines 31-35 of page 5 of the specification as providing descriptive support for 'the upper limit of the protein size at about 140 kDa (i.e., full-length cytotoxin precursor)' and lines 20-23 of page 8 for 'exhibiting no cytotoxic activity or reduced cytotoxic activity'. These parts of the specification respectively are recited herebelow:

> "cytotoxin" or "toxin" of H. pylori refers to the protein, and fragments thereof, whose nucleotide sequence and amino acid sequences are shown in Figs. 1 and 2, respectively, and their derivatives, and whose molecular weight is about 140 kDa. This protein serves as a precursor
>
> nature. Thus, this term also encompasses the situation wherein the H. pylori bacterium genome is genetically modified (e.g., through mutagenesis) to produce one or more altered polypeptides.

These passages from the specification, or the rest of the specification as originally filed, however do not provide descriptive support for the newly added molecular weight ranges and for the purified recombinant polypeptide comprising 'amino acid substitutions' and having a molecular weight falling within the recited range, and exhibiting immunological identifiability by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3 and no cytotoxic activity or reduced cytotoxic activity compared with *Helicobacter pylori* cytotoxin purified from cell cultures. In the instant case, the specification as originally filed did not disclose a molecular weight range for the altered polypeptide having amino acid substitutions exhibiting no cytotoxic activity or reduced cytotoxic activity. Therefore, the limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the

addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or point to specific pages and line numbers in the specification, as originally filed, where support for such recitations can be found.

**18)** Claims 82, 83, 93 and 94 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 82, 83, 93 and 94 include the new limitations: 'immunogenic, purified' recombinant polypeptide of claim ..... having a molecular weight of at least 87 kDa or at least 100 kDa 'to about 140 kDa wherein said polypeptide comprises amino acid substitutions to form an altered polypeptide wherein said altered polypeptide exhibits no cytotoxic activity or reduced cytotoxic activity compared with *Helicobacter pylori* cytotoxin purified from cell cultures'. Accordingly, the claims are now drawn to a purified recombinant polypeptide comprising at least ten or fifteen contiguous amino acids from the amino acid sequence of SEQ ID NO: 3, which polypeptide is *required* to be 'immunogenic' and is required to have a molecular weight falling within the range of at least 87 kDa or at least 100 kDa to about 140 kDa and amino acid substitutions (i.e., any number of substitutions) to form an altered polypeptide which is *required* to exhibit no cytotoxic activity or reduced cytotoxic activity compared with *Helicobacter pylori* cytotoxin purified from cell cultures. Applicants point to lines 19-29 of page 16 of the specification as providing descriptive support for 'the upper limit of the protein size at about 140 kDa (i.e., full-length cytotoxin precursor)' and lines 20-23 of page 8 for 'exhibiting no cytotoxic activity or reduced cytotoxic activity'. These parts of the specification respectively are recited herebelow:

> "cytotoxin" or "toxin" of H. pylori refers to the protein, and fragments thereof, whose nucleotide sequence and amino acid sequences are shown in Figs. 1 and 2, respectively, and their derivatives, and whose molecular weight is about 140 kDa. This protein serves as a precursor
>
> nature. Thus, this term also encompasses the situation wherein the H. pylori bacterium genome is genetically modified (e.g., through mutagenesis) to produce one or more altered polypeptides.

These passages from the specification, or the rest of the specification as originally filed, however do

not provide descriptive support for the newly added molecular weight ranges and for the purified recombinant polypeptide having a molecular weight falling within the recited range, and exhibiting immunogenicity and at the same time having no cytotoxic activity or reduced cytotoxic activity compared with *Helicobacter pylori* cytotoxin purified from cell cultures. Therefore, the limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or point to specific pages and line numbers in the specification, as originally filed, where support for such recitations can be found.

## Rejection(s) under 35 U.S.C. § 102

**19)** Claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 are rejected under 35 U.S.C § 102(b) as being anticipated Manetti *et al.* (*Infect. Immun.* 65: 4615-4619, November 1997) (Manetti *et al.*, 1997).

Instant claims are not granted priority to the PCT application because of the new matter in the claims as identified above, but are granted the filing date of the instant application.

Manetti *et al.* (1997) taught a highly purified VacA cytotoxin of *H. pylori* CCUG17874 which is mildly formaldehyde-inactivated (i.e., toxoided) which induced high titer *H. pylori* cytotoxin-specific antibodies (i.e., immunogenic) in rabbits (see abstract; right column on pages 4615 and 4617). The formaldehyde-treated VacA exhibited reduced toxicity compared with native *H. pylori* cytotoxin purified from the culture supernatant of *H. pylori* CCUG17874 and retained antigenic integrity and reacting with a purified immunoglobulin from a rabbit serum raised against native VacA (see first paragraph under 'Materials and Methods'; Figures 1 and 2; and page 4616). Although Manetti *et al.* (1997) are silent about the molecular weight and the SEQ ID number(s) as recited, and the nucleotides encoding the same as recited, since the prior art polypeptide is produced by the same CCUG 17874 strain of *H. pylori* as that of Applicants' strain (see sections 'Materials and methods' and 'Results' of the instant specification), the prior art polypeptide is expected to necessarily have the same structure as recited and the same molecular weight as recited, absent evidence to the contrary.

The limitation 'recombinant' in the instant claims is viewed as a process limitation in product claims. It should be noted that when claims are drawn to a product-by-process, claims are not limited to the manipulations of the recited step(s), but only the structure implied by the steps. MPEP § 2113 states:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)* (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the isolation process results in a product that is structurally different from the product of the prior art.

Claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 are anticipated by Manetti *et al.* (1997).

**20)** Claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 are rejected under 35 U.S.C § 102(b) as being anticipated by Schmitt *et al.* (*Mol. Microbiol.* 12: 307-319, 1994) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A Laboratory Manual.* Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988, already of record).

Instant claims are not granted priority to the PCT application because of the new matter in the claims as identified above, but are granted the filing date of the instant application. Applicants' statement on page 7 of their amendment/response filed 04/04/05 that the polypeptide having the amino acid sequence of SEQ ID NO: 3 *is not itself cytotoxic* has been noted.

Schmitt *et al.* taught a purified polypeptide comprising several stretches of at least 5, 10 or15 contiguous amino acids, AFFTTVIIPAIVGGIATG;
WGLKQAEEANKTPDKPDKVWRIQAGKGFNEFPNKEYDLY;
SLLSSKIDGGWDWGNAARHYWVK etc. of the instantly recited SEQ ID NO: 3. The sequences placed in open boxes are identical to the *published* N-terminal sequence of *H. pylori* vacA of Cover and Blaser, 1992. The polypeptide is encoded by the *H. pylori vacA* gene. See the 1291 residues-long amino acid sequence depicted in Figure 3 and the corresponding nucleotide sequence. This polypeptide is the 139.6 kDa (i.e., about 140 kDa) precursor VacA molecule, which forms a mature cytotoxin *only* upon specific proteolytic cleavage (see Summary; Figure 7; left column of page 308;

pages 309, 311, 314 and 316). That the prior art precursor VacA polypeptide itself is not cytotoxic is inherent from the teachings of Schmitt *et al.* Schmitt's polypeptide comprising multiple 5, 10, 15, or more than 15 amino acid-long fragments, is long enough to serve inherently as an antigen or immunogen and is capable of specifically immunoreacting with an antibody specific to the polypeptide having the amino acid sequence of SEQ ID NO: 3, since it is well known in the art that the smallest peptides which elicit antibodies that bind to the original full length protein are 6 amino acids in length. See the first sentence under 'Size of the Peptide' on page 76 of Harlow *et al.* By having at least two amino acid substitutions at positions 52 and 62 compared to the instantly recited SEQ ID NO: 3 (see Figure 3 of Schmitt *et al.* and Applicants' Figure 2), Schmitt's polypeptide also qualifies and inherently serves as a non-toxic altered polypeptide having a molecular weight of about 140 kDa.

Claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 are anticipated by Schmitt *et al.* The reference of Harlow *et al.* is not used as a secondary reference in combination with Schmitt *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Schmitt *et al.* with the unrecited limitation(s) being inherent in view of what is known in the art as explained above. See *In re Samour* 197 USPQ 1 (CCPA 1978).

The limitation 'recombinant' in the instant claims is viewed as a process limitation in product claims. It should be noted that when claims are drawn to a product-by-process, claims are not limited to the manipulations of the recited step(s), but only the structure implied by the steps. MPEP § 2113 states:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)* (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the isolation process results in a product that is structurally different from the product of the prior art.

**21)** Claims 40, 54, 63-65, 74, 75 and 84-86 are rejected under 35 U.S.C. § 102(b) as being anticipated by Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992 – already of record)

(Cover *et al.*, 1992).

Instant claims are not afforded the priority benefit to PCT application(s), or to the foreign priority application, FI 92A000052 filed 03/02/92, since these applications lack descriptive support for the limitations: 'compared with *Helicobacter pylori* cytotoxin purified from cell cultures', and/or for a purified polypeptide or recombinantly produced polypeptide comprising the amino acid sequence of SEQ ID NO: 3, having the two *required* functional properties of: (a) immunological identifiability by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3 *and*, (b) no cytotoxic activity or reduced cytotoxic activity compared with *Helicobacter pylori* cytotoxin purified from cell cultures.

It is noted that the transitional recitation 'comprising' represents open-ended claim language and therefore does not exclude additional, unrecited elements. See MPEP 2111.03 [R-1].

Cover *et al.* (1992) taught an immunogen comprising an isolated denatured *Helicobacter pylori* protein having a molecular weight of 87,000 which elicited antibodies to the protein on immunization of rabbits (see first full paragraph in right column on page 10571; and right column on page 10574). The protein comprised a 23 amino acid-long amino terminal portion having the sequence, AFFTTVIIPAIVGGIATGTAVGT, which amino terminal sequence has 100% sequence identity with a 23 amino acid-long contiguous polypeptide fragment that stretches between positions 34-56 of the instantly recited SEQ ID NO: 3 (see the very first sequence depicted at the top portion of Cover's Table III). The denatured immunogenic protein of the prior art comprising the N-terminal sequence AFFTTVIIPAIVGGIATGTAVGT is expected to have the inherent ability to be immunologically identifiable by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3 and is expected to have reduced cytotoxic activity compared with *Helicobacter pylori* cytotoxin purified from cell cultures.

The term 'recombinant' or 'expressed from ..... nucleotides of SEQ ID NO: 2' in the instant claims represents a process limitation in product claims. The prior art polypeptide anticipates the instantly claimed polypeptide, irrespective of how it is obtained. When claims are drawn to a product-by-process, claims are not limited to the manipulations of the recited step(s), but only the structure implied by the steps. MPEP § 2113 states:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior

> art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)* (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the process results in a product that is structurally different from the product of the prior art. In the instant case, Applicants have not shown that the underlying structure of the prior art polypeptide comprising the above-identified 23 amino acid-long N-terminal fragment differs from the instantly recited at least 5, 10, or 15 contiguous amino acid-containing polypeptide of the amino acid sequence SEQ ID NO: 3 comprising the same structurally identical N-terminal fragment.

Claims 40, 54, 63-65, 74, 75 and 84-86 are anticipated by Cover *et al.* (1992).

## Remarks

**22)** Claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 stand rejected.

A purified polypeptide comprising the amino acid sequence of SEQ ID NO: 3 is free of prior art currently of record.

**23)** Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

**24)** Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses and/or papers is (703) 872-9306.

**25)** Information regarding the status of an application may be obtained from the Patent

Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**26)** Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

June, 2005

SD

S. DEVI, PH.D.
PRIMARY EXAMINER